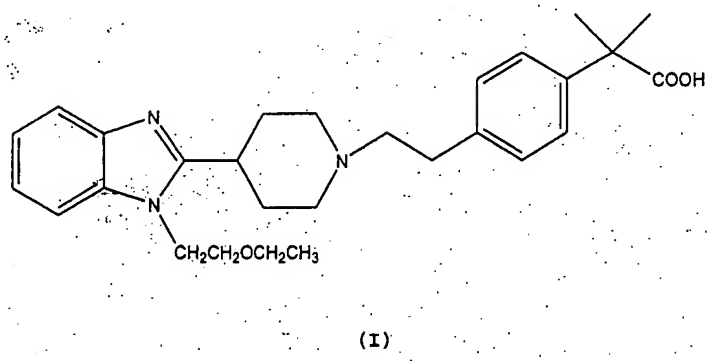
10/511822
DT05 Rec'd PCT/PTO 19 OCT 2004

Polymorph of 4-[2-[1-(2-ethoxyethyl)-1H-benzidimazole-2-yl]-1-piperidinyl]ethyl]-αα-dimethyl-benzenoacetic acid

Area of the invention

The invention refers to a new polymorphous crystalline form of 4-[2-[1-(2-ethoxyethyl)-1H-benzidimazole-2-yl]-1-piperidinyl]ethyl]-αα-dimethyl-benzeno-acetic acid (herein referred to as "bilastin") of formula (I).



(I)

From hereon referred to as polymorph 1, to procedures used to prepare it, to pharmaceutical formulae that contain polymorph 1 and to the use of polymorph 1 to treat allergic reactions and pathological processes mediated by histamine in mammals, such as man.

Background of the Invention

US patent number 5,877,187 confers the rights to bilastin, a preparation with antihistaminic properties without sedative or cardiovascular effects. This patent also concerns a procedure to prepare bilastin and the use of this preparation to treat allergic reactions in mammals but it does not include or suggest the possible existence of polymorphic forms of this compound.

To prepare pharmaceutical preparations containing bilastin for their administration in mammals and especially in man, in accordance with international health authority specifications, bilastin must be manufactured in the most stable crystalline form possible, especially in a form that has constant physical properties.

Summary of the Invention

We have found that bilastin can exist in three different crystalline polymorphic forms, each with different physical properties.

The invention refers to a pure crystalline form of polymorph 1 of bilastin, characterised by X-ray chromatographic analysis, with approximate crystal parameters as follows:

Crystallograph system	Monoclinical	
Spatial group	P2 (1)/c	
Crystal size	0.56 x 0.45 x 0.24 mm	
Cell dimension	a=23.38 (5) A angstrom	$\alpha = 90°$
	b=8.829 (17) A	$\beta = 90°$
	c=12.59 (2) A	$\gamma = 90°$
Volume	2600 A^3	
Z, calculated density	4, 1.184 mg/m^3	

The crystalline polymorph 1 of bilastin is also characterised by its infrared absorption spectrum in potassium bromide tablet that has the following characteristic absorption bands, expressed in reciprocal centimetres:

3430 (s)*; 3057 (w)*; 2970 (s); 2929 (s); 2883 (m)*; 2857 (m); 2797 (w); 1667 (m); 1614 (m); 1567 (w); 1509 (s); 1481 (m); 1459 (vs)*; 1431 (m); 1378 (w); 1346 (m); 1326 (m); 1288 (w); 1254 (m); 1199 (w); 1157 (w); 1121 (vs); 1045 (w); 1020 (w); 1010 (w); 991 (w); 973 (w); 945 (w); 829 (w); 742 (s); 723 (w); 630 (w), * where (w) = weak intensity, (m)= medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 1 represents the infrared spectrum of the crystalline polymorph 1 of the bilastin in a potassium bromide tablet recorded in a Fourier Perkin Elmer Spectrum One transformer spectrophotometer.

Brief description of the figures

Figure 1 shows a typical infrared absorption spectrum in potassium bromide of polymorph 1. (Vertical axis: Transmission (%); Horizontal axis: Band number (cm^{-1})).

Figure 2 shows a typical infrared absorption spectrum in potassium bromide of polymorph 2. (Vertical axis: Transmission (%); Horizontal axis: Band number (cm^{-1})).

Figure 3 shows a typical infrared absorption spectrum in potassium bromide of polymorph 3. (Vertical axis: Transmission (%); Horizontal axis: Band number (cm^{-1})).

Detailled description of the invention

We have found that bilastin can exist in three clearly different polymorphic forms called polmorph 1, polymorph 2 and polymorph 3.

The procedure described in US patent no. 5,877,187 generates a mixture of polymorphs 2 and 3. We have discovered experimental conditions and specific solvents to produce clearly different polymorphic forms of bilastin. The crystalline polymorph 1 of pure bilastin is prepared according to the procedures of this invention. The polymorphic forms 1 and 2 are stable. Polymorph 3 is not very stable and is difficult to obtain in the pure form. Both polymorph 2 and polymorph 3 are converted into polymorph 1 for the purposes of this invention.

Polymorph 1 of bilastin has a melting point of 200.3°C. Polymorph 2 has a melting point of 205.2°C. Polymorph 3 has a melting point of 197.0°C.

The crystalline polymorphic form 1 of bilastin is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimetres:

3430 (s)*; 3057 (w)*; 2970 (s); 2929 (s); 2883 (m)*; 2857 (m); 2797 (w); 1667 (m); 1614 (m); 1567 (w); 1509 (s); 1481 (m); 1459 (vs)*; 1431 (m);1378 (w); 1346 (m); 1326 (m); 1288 (w); 1254 (m); 1199 (w); 1157 (w); 1121 (vs); 1045 (w); 1020 (w); 1010 (w); 991 (w); 973 (w); 945 (w); 829 (w); 742 (s); 723 (w); 630 (w), * where (w) = weak intensity, (m)= medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 1 represents the infrared spectrum of the crystalline polymorph 1 of the bilastin in a potassium bromide tablet recorded in a Fourier Perkin Elmer Spectrum One transformer spectrophotometer.

The crystalline polymorphic form 2 of bilastin is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimetres:

3429 (s)*; 3053 (w)*; 2970 (s)*; 2932 (s); 2868 (s); 2804 (w); 1699 (m); 1614 (m)*; 1567 (m); 1508 (s); 1461 (vs)*; 1381 (m); 1351 (s); 1331 (m); 1255 (m); 1201 (w); 1156 (m); 1121 (vs); 1048 (w); 995 (w); 823 (w); 767 (w); 744 (s); 724 (d); 630 (w), * where (w) = weak intensity, (m)= medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 2 represents the infrared spectrum of the crystalline polymorph 2 of bilastin in a potassium bromide tablet recorded in a Fourier Perkin Elmer Spectrum One transformer spectrophotometer.

The crystalline polymorphic form 3 of bilastin is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimetres:

3430 (s)*; 3053 (w)*; 2970 (s); 2932 (s); 2868 (s); 2804 (w); 1921 (w); 1708 (m)*; 1614 (m); 1568 (m); 1508 (s); 1461 (vs)*; 1380 (m); 1351 (m); 1330 (m); 1271 (m); 1255 (m); 1201 (w); 1156 (m); 1121 (vs); 1048 (w); 995 (w); 823 (m); 767 (w); 744 (s); 724 (w); 630 (w), * where (w) = weak intensity, (m)= medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 3 represents the infrared spectrum of the crystalline polymorph 3 of the bilastin in a potassium bromide tablet recorded in a Fourier Perkin Elmer Spectrum One transformer spectrophotometer.

We have discovered that, in selected experimental conditions, the mixture of the polymorphic forms 2 and 3, obtained according to US patent no. 5,877,187, is surprisingly transformed into polymorph 1. We have also discovered that polymorph 1 of bilastin is very stable and is not transformed into any of the other polymorphs 2 and 3. Similarly, in the same experimental conditions, the pure polymorphic form 2 of bilastin is surprisingly transformed

into the pure polymorphic form 1. Polymorphic form 3, which is the most unstable, undergoes the same transformation in the same conditions.

Polymorph 1 of bilastin is a very stable polymorph at room temperature and is, therefore, very useful as an active ingredient of a pharmaceutical preparation. Polymorph 1 is also stable when stored at temperatures above room temperature.

The polymorphic crystalline form 1 of bilastin is characterised by the following data of its X-ray crystallographic analysis as a monocrystal, with crystal parameters of approximately the following values:

Crystallograph system	Monoclinical	
Spatial group	P2 (1)/c	
Crystal size	0.56 x 0.45 x 0.24 mm	
Cell dimension	a=23.38 (5) A angstrom	$\alpha = 90^{\circ}$
	b=8.829 (17) A	$\beta = 90^{\circ}$
	c=12.59 (2) A	$\gamma = 90^{\circ}$
Volume	2600 A^3	
Z, calculated density	4, 1.184 mg/m^3	

During the development of polymorph 1 of bilastin for pharmaceutical preparations, elaborated according to correct manufacturing procedures, we have discovered that crystallization of bilastin (prepared according to the description given in US patent no. 5,877,187) of short chained alcohols, preferably isopropylic alcohol and n-butanol and its mixtures, leads to generation of the pure polymorphic form 1 of bilastin with a high yield. Crystallisation of acetone, dimethylsulphoxide, dimethylformamide, acetonitrile and tetrahydrofurane or its mixtures also lead to generation of

polymorph 1, although with lower yields. It is, therefore, preferable to use the former solvents.

The infrared spectrum of polymorph 1 of bilastin in potassium bromide is characterised by the following bands, absent from polymorphs 2 and 3:

Wavelength (cm^{-1})
3057
2929
2883
2857
2797
1667
1481
1431
1346
1326
1288
973
945
829

Figure 1 shows the complete infrared spectrum of polymorph 1 of bilastin in potassium bromide, recorded with a Fourier Perkin Elmer Spectrum One transformer spectrophotometer.

Pharmaceutical preparations

Pharmaceutical preparations of this invention can contain, as well as an effective quantity of polymorph 1 of bilastin as an active ingredient as an antiallergic or antihistaminic agent, several pharmaceutically acceptable excipients that can be solid or liquid. The solid pharmaceutical preparations include powders, tablets, dispersible granules, capsules, stamps and suppositories. A solid excipient can be one of several substances that act as diluents, aromatising agents, agglutinants or disintegrating agents and an encapsulation material. The powders and tablets preferentially contain from approximately 5 to approximately 20 per cent of the active ingredient. Appropriate solid excipients are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, waxes with low melting point, cocoa butter and similar products. The term "preparations" includes the formulation of the active ingredient with an excipient for encapsulation to produce a capsule in which the active ingredient (with or without other excipients) is surrounded with the excipient by an encapsulation material. Tablets, powders, stamps and capsules can be used as suitable forms for oral administration. The active ingredient can also be incorporated into a chewing gum that can contain sweeteners, flavorings and colorings as appropriate.

To prepare suppositories, a compound with a low melting point, such as a mixture of fatty acid glycerides or cocoa butter, is melted and the active ingredient is mixed well and homogeneously dispersed in the mixture. The homogeneous melted mixture is placed in the appropriate moulds and left to cool until it solidifies.

Liquid preparations include suspensions, lotions and emulsions. An example of these corresponds to aqueous suspensions that can be made by mixing

the finely divided active ingredient in water with suspension agents. Aqueous solutions can be prepared by placing the active ingredient in water and adding suitable coloring agents, aromas, stabilising agents, sweeteners, solubilising and thickening agents as appropriate.

Also, topical preparations are considered for nasal, ophthalmic and dermal use. Appropriate formulae for nasal administration can correspond to solutions or suspensions. Ophthalmic formulae can be lotions, suspensions or ointments. Dermal preparations can be lotions, suspensions, ointments and creams. Ointments usually contain lipophylic excipients such as mineral oil or vaseline. Solutions for ophthalmic use can contain sodium chloride, acid and/or base to adjust the pH, and purified water and preservatives.

Similarly, a compound is being contemplated for transdermic use, consisting of a therapeutically effective amount of active ingredient incorporated into an excipient that corresponds to a liquid, a gel, a solid matrix or an adhesive patch sensitive to pressure, to be released via a transdermic administration system.

The effective antiallergic or antihistaminic amount of polymorph 1 of bilastin for topical administration varies between 0.1 and 5% of the total weight of the pharmaceutical compound. The preferred amount ranges from 0.1 to 2% of the total weight of the pharmaceutical compound.

The effective antiallergic or antihistaminic amount of polymorph 1 of bilastin for oral administration varies from 1 to 50 mg/day, with preferably an amount corresponding to approximately 2 to 20 mg/day in a single or fractionated doses.

Polymorph 1 of bilastin has antihistaminic properties that have been demonstrated in experimental pharmacological models, such as preventing histamine-induced lethality in the guinea-pig and antagonism against cutaneous capillary permeability induced by histamine in the rat.

The following examples illustrate but do not limit the scope of the present invention.

EXAMPLE 1

Preparation of polymorph 1 of bilastin.

Dissolve bilastin (see the US patent no. 3,877,187) in isopropylic alcohol heated to reflux for approximately 15-20 minutes under nitrogen while stirring. Cool the solution to 50°C over 6 hours and stop stirring. Let the solution cool to room temperature and stir again for three hours, filter and wash with cold isopropylic alcohol. Dry the solid residue in a vacuum cabinet at 35-40°C to constant weight.

EXAMPLE 2

Preparation of polymorph 1 of bilastin.

Heat a suspension of bilastin (see US patent no. 5,877,187) in n-butanol and reflux for 3 hours under nitrogen while stirring. Leave the solution to cool while stirring, filter off the solid residue and dry it in a vacuum chamber at 35-40°C to constant weight.

EXAMPLE 3

Preparation of polymorph 1 of bilastin.

Treat a mixture of polymorphs 2 and 3 of bilastin for several hours with hot acetone. Let the mixture cool to room temperature and filter off the solid residue. Dry it to constant weight.

EXAMPLE 4

Preparation of polymorph 1 of bilastin.

Dissolve polymorph 3 of bilastin in isopropylic alcohol heated to reflux and stir for approximately 15-20 minutes under nitrogen. Let the solution reach room temperature constantly stirring, filtering and washing with cold isopropanol. Dry the solid in a vacuum chamber at 35-40°C to constant weight.

EXAMPLE 5

Preparation of polymorph 1 of bilastin.

Dissolve polymorph 2 of bilastin in n-butanol heated to reflux while stirring for approximately 3 hours. Let the solution reach room temperature while stirring, filtering and draining. Dry the solid in a vacuum chamber at 35-40°C to constant weight.